

TITLE OF THE INVENTION

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N-ALKYL ASPARTYL DIPEPTIDE ESTER COMPOUNDS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a novel N-alkylaspartyl dipeptide ester compounds, a sweetening agent or a sweetened food or similar products comprising the compound as an effective component. The invention further provides methods of imparting sweetness in a product and methods of making the N-alkylaspartyl dipeptide ester compounds.

Discussion of the Background

In recent years, as eating habits and products eaten have changed, fatness caused by excessive sugar intake and diseases caused by fatness have been of significant concern. Accordingly, the development of a low-calory sweetener (sweetening agent) that replaces sugar has been in demand. A sweetener that has been widely used is aspartame which is excellent in safety, quality of sweetness and taste properties. However, there are problems with aspartame with respect to its stability. WO 94/11391 states that compounds in which an alkyl group is introduced on a nitrogen atom of aspartic acid in the aspartame markedly improves the sweetening potency and also results in a slight improvement in the stability of the compound. The best compound described in WO 94/11391 is N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine 1-methyl ester having a 3,3-dimethylbutyl group as an alkyl group and which has a sweetening potency of 10,000 times that of sucrose (the value is obtained by comparing the compound to 2%, 5% and 10% sucrose solutions).

Aspartame compounds having 20 different substituents other than the 3,3-dimethylbutyl group are also disclosed where the compounds have sweetening potencies less than 2,500 times that of sucrose. Compounds having a 3- (substituted phenyl) propyl group as an alkyl group are also shown. Among these, N-[N-(3-phenylpropyl)-L- (α -aspartyl]-L-phenylalanine 1-methyl ester and N-[N-(3-(3-methoxy-4-hydroxyphenylpropyl)-L- α -aspartyl]-L-phenylalanine 1-methyl ester are described as having sweetening potencies of

1500 and 2500 times that of sucrose, respectively. These sweetening potencies are far less than that of N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine 1-methyl ester, which is 10,000 times that of sucrose. Further described are N-[N-[(RS)-3-phenylbutyl]-L-(α -aspartyl]-L-phenylalanine 1-methylester, which has as an alkyl group a 3-phenyl propyl group to the third position of which a methyl group is introduced, that is a 3-phenyl butyl group, is reported to have a sweetening potency of 1,200 times that of sucrose. The N-[N-(3-phenylpropyl)-L- α -aspartyl]-L-phenylalanine 1-methyl ester has a lower sweetening potency due to the methyl group introduced at the third position.

5 Furthermore, N-[N-[3-(3-methoxy-4-hydroxyphenyl)(RS)-1-methylpropyl]-L-a-aspartyl]-L-phenylalanine 1-methyl ester, having a structure corresponding to N-[N[3-(3-methoxy-4-hydroxyphenyl) propyl] -L-(α -aspartyl]-L-phenylalanine 1-methyl ester, with a methyl group on the first position of the propyl group is reported to have a sweetening potency of 500 times that of sucrose. The significantly lower sweetening potency is due to the methyl group on the the propyl group.

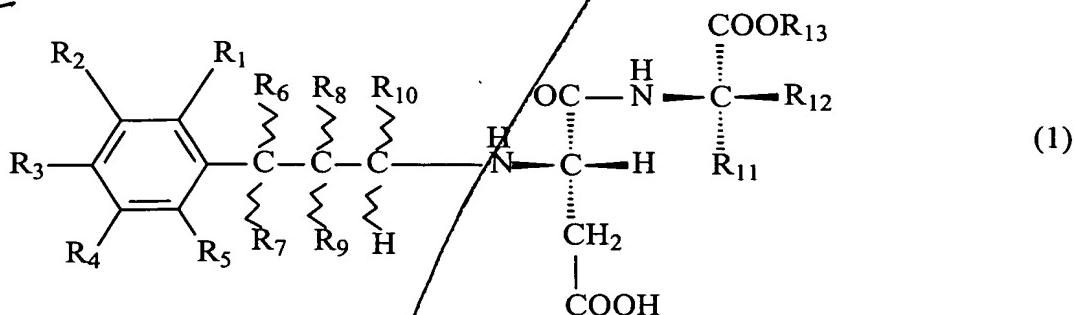
10 Another example of replacing the L-phenylalanine methyl ester moiety with another amino acid ester is N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-tyrosine 1-methyl ester which has a sweetening potency of 4,000 times that of sucrose.

15 In view of the foregoing, development of a low-calory sweetener having a superior sweetening potency is in demand.

20 Thus, the present inventors sought to solve the long-standing problems associated with prior low-calory sweeteners and provide novel N-alkylaspartyl dipeptide ester compounds which are excellent in safety and which have sweetening potencies equal to or higher than that of N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L phenylalanine 1-methylester, and a low-calory sweetening agent comprising the compound as an effective component.

SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is an N-alkylaspartyl dipeptide ester compound, and salts thereof, represented by formula (1):



wherein R₁, R₂, R₃, R₄ and R₅ are independent from each other, selected from the group consisting of a hydrogen atom, a hydroxyl group, an alkoxy group having 1 to 3 carbon atoms, an alkyl group having 1 to 3 carbon atoms and a hydroxy alkyloxy group having two or three carbon atoms, and R₁ and R₂, or R₂ and R₃, optionally, form a methylene dioxy group, and R₄ and R₅, and R₁ or R₃ which do not form the methylene dioxy group are defined as above:

R_6 , R_7 , R_8 , R_9 and R_{10} are independent from each other, a hydrogen atom or an alkyl group with 1 to 3 carbon atoms; and optionally, two of R_6 , R_7 , R_8 , R_9 and R_{10} may combine to form an alkylene group with 1 to 5 carbon atoms, and R_6 , R_7 , R_8 , R_9 and R_{10} which do not form the alkylene group with 1 to 5 carbon atoms are defined as above;

R_{11} is selected from the group consisting of a hydrogen atom, a benzyl group, a p-hydroxy benzyl group, a cyclohexyl methyl group, a phenyl group, a cyclohexyl group, a phenyl ethyl group and a cyclohexyl ethyl group;

R_{12} is selected from the group consisting of a hydrogen atom and an alkyl group with 1 to 3 carbon atoms; and

R_{13} is selected from the group consisting of alkyl groups with 1 to 4 carbon atoms;

with the proviso that the following are excluded:

where R_6 , R_7 , R_8 , R_9 and R_{10} are a hydrogen atom at the same time,

where R₆ is a methyl group, R₁, R₂, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ and R₁₂ are a hydrogen atom at the same time and R₁₁ is a benzyl group or a p-hydroxy benzyl group, at the same time; and

where R₂ or R₄ are methoxy groups, R₃ is a hydroxyl group, R₁₀ is a methyl group, R₁,

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~~R₄, R₅, R₆, R₇, R₈ and R₉ are a hydrogen atom at the same time, and R₁₁ is a benzyl group or a p-hydroxybenzyl group.~~

Other objects of the present inventions include compositions comprising the N-alkylaspartyl dipeptide ester compound, methods of imparting sweetness into a substance by adding the N-alkylaspartyl dipeptide ester compound to the substance and methods of making the N-alkylaspartyl dipeptide ester compound.

DETAILED DESCRIPTION OF THE INVENTION

Each document, patent application or patent publication cited by or referred to in this disclosure is incorporated by reference in its entirety.

For resolving the above problem, the present inventors have synthesized a variety of compounds in which a variety of 3-(substituted phenyl) propyl group, such as 3,3-dialkyl-3-(substituted phenyl) propyl groups or (RS)-3-alkyl-3-(substituted phenyl) propyl groups, have been introduced on a nitrogen atom of an aspartic acid constituting an aspartame and an aspartame compound, by reductive alkylation, using a 3-phenylpropionaldehyde compound, a cinnamaldehyde compound, a (2-phenylethyl) alkyl ketone compound or the like having a variety of substituents on a phenyl group and also having 1 to 4 alkyl substituents on the main chain, and examined the sweetening potency of these compounds. The compound corresponds to the aspartame the L-phenylalanine methyl ester moiety of which is substituted by another amino acid ester therein. As a result of our investigations, the sweetening potency of some of the aspartame compounds is much higher in sweetening potency than N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L phenylalanine 1-methylester reported to have the sweetening potency of 10000 times that of sucrose, to say nothing of N-[N-[(RS)-3-phenylbutyl]-L-(α -aspartyl]-L-phenylalanine 1-methylester reported to have the sweetening potency of 1200 times that of sucrose or N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-tyrosine 1-methylester reported to have a sweetening potency equal to 4000 times that of sucrose, as disclosed in the international Patent Publication WO 94/11391, and that, in particular, the compound represented by the general formula (1) below is superior as a sweetening agent.

The novel N-alkylaspartyl dipeptide ester compound according to the present invention includes compounds represented by the above formula (1) and salts thereof. Preferably, the amino acids in the compound of formula (1), aspartic acid, is in the L- isomer. Other amino acids may be in the L- or D-isomer, as desired.

In the compounds of the present invention substituents are defined as known in the art and include a hydrogen atom (H), a hydroxyl group (OH), an alkoxy group with 1 to 3 carbon atoms (OCH_3 , OCH_2CH_3 , $\text{OCH}_2\text{CH}_2\text{CH}_3$, etc.), an alkyl group with 1 to 3 carbon atoms (CH_3 , CH_2CH_3 , $\text{CH}_2\text{CH}_2\text{CH}_3$, etc.), a hydroxy alkyloxy group with two or three carbon atoms ($\text{O}(\text{CH}_2)\text{OH}$, $\text{OCH}_2\text{CH(OH)CH}_3$, etc.), a methylene dioxy group (OCH_2O) and an alkylene group with 1 to 5 carbon atoms (such as CH_2 , CH_2CH_2 , $\text{CH}_2\text{CH}_2\text{CH}_2$ and so forth).

Preferred substituents in the compounds of formula (1) include:

(1) R_6 is a methyl group.

(2) R_7 is a methyl group.

(3) R_8 , R_9 and R_{10} are hydrogen atoms.

(4) R_{10} is a methyl group.

(5) R_6 and R_7 combine to form an alkylene group having 1 to 5 carbon atoms.

(6) Above compounds (1), not containing the compounds wherein R_1 , R_2 , R_3 , R_4 and

R_5 are hydrogen atoms.

(7) R_6 is a methyl group and R_1 , R_2 , R_3 , R_4 , R_5 , R_7 , R_8 , R_9 and R_{10} are hydrogen atoms.

(8) R_6 is an alkyl group having two or three carbon atoms.

(9) Two of R_6 , R_7 , R_8 , R_9 and R_{10} combined to form an alkylene group with one to five carbon atoms.

(10) R_6 , R_7 , R_8 , R_9 are hydrogen atoms, R_{10} is a methyl group, R_2 is a hydrogen atom; a hydroxyl group; an alkoxy group with two or three carbon atoms, an alkyl group with one to three carbon atoms, a hydroxy alkyloxy group having two or three carbon atoms; or R_2 combined with R_1 or R_3 is a methylene dioxy group.

(11) R_6 , R_7 , R_8 and R_9 are hydrogen atoms, R_{10} is a methyl group, R_3 is a hydrogen atom, an alkoxy group with one to three carbon atom, an alkyl group with one to three carbon atoms and a hydroxy alkyloxy group having two or three carbon atoms; and R_2 may combine with R_1 or R_3 form a methylene dioxy group.

(12) R_1 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are hydrogen atoms, R_{10} is a methyl group, R_2 is a methoxy group, R_3 is a hydroxyl group, and R_{11} is a hydrogen atom, a cyclohexyl methyl group, a phenyl group, a cyclohexyl group, a phenylethyl ($\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$) and a cyclohexylethyl group ($\text{CH}_2\text{CH}_2\text{C}_6\text{H}_{11}$).

(13) R_6 and R_7 , are hydrogen atoms and R_{10} is an alkyl group with two or three carbon atoms.

(14) R₆ and R₇ are hydrogen atoms and two of R₈, R₉ and R₁₀ may combine to form an alkylene group with 1 to 5 carbon atoms.

(15) R₆, R₇ and R₁₀ are hydrogen atoms, at least one of R₈ and R₉ is an alkyl group with one to three carbon atoms or R₈ and R₉ combine to form an alkylene group with 1 to 5 carbon atoms.

(16) R₃ is a methoxy group, R₁, R₂, R₄, R₅, R₇, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆ and R₁₃ are a methyl groups and R₁₁ is a benzyl group.

(17) R₂ is a hydroxyl group, R₁, R₃, R₄, R₅, R₇, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆ and R₁₃ is a methyl group, and R₁₁ is a benzyl group.

(18) R₂ is a methoxy group, R₃ is a hydroxyl group, R₁, R₄, R₅, R₇, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(19) R₂ is a hydroxyl group, R₃ is a methoxy group, R₁, R₄, R₅, R₇, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(20) R₂ is a methoxy group, R₃ is a hydroxyl group, R₁, R₄, R₅, R₇, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆ and R₁₃ are methyl groups and R₁₁ is a p-hydroxybenzyl group.

(21) R₂ is a hydroxyl group, R₃ is a methoxy group, R₁, R₄, R₅, R₇, R₈, R₉, R₁₀ and R₁₂ is a hydrogen atom, R₆ and R₁₃ are methyl groups and R₁₁ is a cyclohexylmethyl group.

(22) R₃ is a methoxy group, R₁, R₂, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆, R₇ and R₁₃ are a methyl groups, and R₁₁ is a benzyl group.

(23) R₃ is a hydroxyl group, R₁, R₂, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen atom,s R₆, R₇ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(24) R₂ is a methoxy group, R₃ is a hydroxyl group, R₁, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen groups, R₆, R₇ and R₁₃ are methyl group sand R₁₁ is a benzyl group.

(25) R₂ is a hydroxyl group, R₃ is a methoxy group, R₁, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen groups, R₆, R₇ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(26) R₂ is a methyl group, R₃ is a hydroxyl group, R₁, R₄, R₅, R₇, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(27) R₂ is a hydroxyl group, R₃ is a methoxy group, R₁, R₄, R₅, R₆, R₇, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₈ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(28) R₁ is a hydroxyl group, R₂, R₃, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆, R₇ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(29) R₁ is a hydroxyl group, R₃ is a methoxy group, R₂, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are

hydrogen atoms, R₆, R₇ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(30) R₁ is a hydroxyl group, R₃ is a methyl group, R₂, R₄, R₅, R₆, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆, R₇ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

5 (31) R₂ and R₃ combine to form a methylene dioxy group, R₁, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆, R₇ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(32) R₂ is a methyl group, R₃ is a methoxy group, R₁, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆, R₇ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(33) R₂ is a methyl group, R₃ is a hydroxyl group, R₁, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆, R₇ and R₁₃ are methyl groups, and R₁₁ is a benzyl group.

10 (34) R₂ is a hydroxyl group, R₃ is a methyl group, R₁, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆, R₇ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(35) R₂ is a methoxy group, R₃ is a hydroxyl group, R₁, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen groups, R₆ and R₇ combine to form a tetramethylene group, R₁₁ is a benzyl group and R₁₃ is a methyl group.

(36) R₂ is a hydroxyl group, R₃ is a methoxy group, R₁, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆ and R₇ are methyl groups, R₁₁ is a benzyl group and R₁₃ is an ethyl group.

(37) R₂ and R₃ are hydroxyl groups, R₁, R₄, R₅, R₈, R₉, R₁₀ and R₁₂ are hydrogen atoms, R₆, R₇ and R₁₃ are methyl groups, and R₁₁ is a benzyl group.

(38) R₂ is a hydroxyl group, R₃ is a methoxy group, R₁, R₄, R₅, R₈, R₉ and R₁₀ are hydrogen atoms, R₆, R₇, R₁₂ and R₁₃ are methyl groups and R₁₁ is a benzyl group.

(39) In the compounds of formula (1), particularly with substituents listed in (16) through (21) and (26) the carbon atom to which R₈ is linked is in the (R), (S), (RS) configuration or the like.

25 (40) In the compounds of formula (1), particularly with substituents listed in (27) the carbon atom to which is R₈ linked in the formula is in the (R), (S), (RS) configuration or the like.

(41) The carbon atom to which R₁₀ is linked in the formula (1) is in the (R), (S), (RS) configuration or the like.

30 Compositions according to the present invention contain one or more of the compounds of formula (1). When the compounds (including compounds in the present invention and the salts thereof) of the present invention are used as sweeteners, these may of

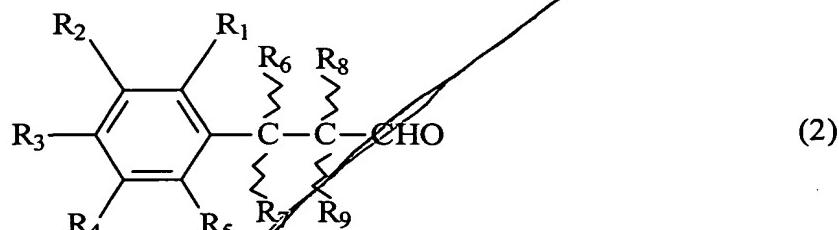
course be used in combination with other sweeteners as desired or needed.

Additional embodiments of the present invention include compositions containing the compound of formula (1) where such compositions contain additives, stabilizers, carriers and the like which are commonly used in the art.

When the compounds of the present invention are used as sweeteners, an appropriate carrier and/or an appropriate bulking agent may be used as required. For example, a carrier, a bulking agent or the like which is known in the art and so far used for the sweeteners is available. The appropriate carriers or bulking agent may be selected from polydextrose, starch, maltodextrines, cellulose, methylcellulose, carboxymethylcellulose and other cellulose compounds, sodium alginate, pectins, gums, lactose, maltose, glucose, sucrose, leucine, glycerole, mannitol, sorbitol, xylitol, erythritol, and equivalents thereof.

The compounds of the present invention can be used as sweeteners or ingredients therefor, and further as sweeteners for products such as foods, beverages and the like to which a sweetness has to be imparted. Examples of such products include soft-drinks, fruit juices, teas, water, confectioneries, chewing gum, hygiene products, toiletries, cosmetics, pharmaceutical products and veterinary products for animals. Still further, they can be used as a form of products having sweetness including the compounds of the present invention and they can be used in a method of imparting sweetness to the products requiring sweetness. The method therefor can be, known methods for example, conventional methods for using a sweetening ingredient for a sweetener in the sweeteners or the method of imparting sweetness. Accordingly, a preferred embodiment of the present invention is a method of imparting sweetness in a substance or a product by adding one or more of the compounds of formula (1) to said substance or product. Such substances or products include those described above.

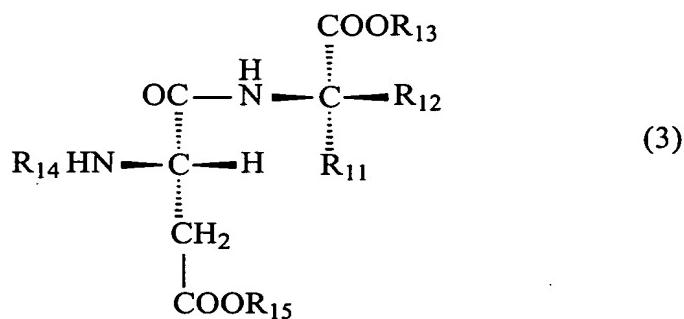
Deek B1 The compound of formula (1), where R_{10} is a hydrogen atom, can be prepared by reacting under reductive alkylation conditions, an aldehyde having the formula (2):



where R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 have the same meaning as R_1 , R_2 , R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 , respectively in the above formula (1); and if R_6 and R_7 , or R_8 and R_9 , are not the same substituents, there is no particular limitation to the configuration of carbon atoms to which R_6 and R_7 , or R_8 and R_9 are linked, such that it may be (R), (S), (RS) or the like whichever is desired;

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with an aspartame compound shown by the following general formula (3):



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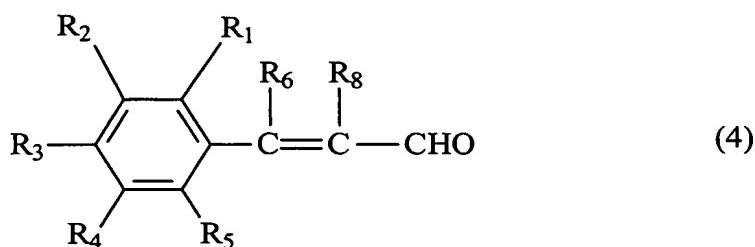
wherein R_{11} , R_{12} and R_{13} in the above formula (3) have the same meaning as R_{11} , R_{12} and R_{13} , respectively in the above formula (1), R_{14} denotes a hydrogen atom or a substituent that can be converted into a hydrogen atom under the reductive alkylation condition and R_{15} denotes a hydrogen atom, a benzyl group or a substituent that may be used for protecting a carboxyl group such as a t-butyl group or the like.

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The compound of formula (1), where R_7 , R_9 and R_{10} are hydrogen atoms can be prepared by reacting under reductive alkylating conditions, an aldehyde having the formula

(4)

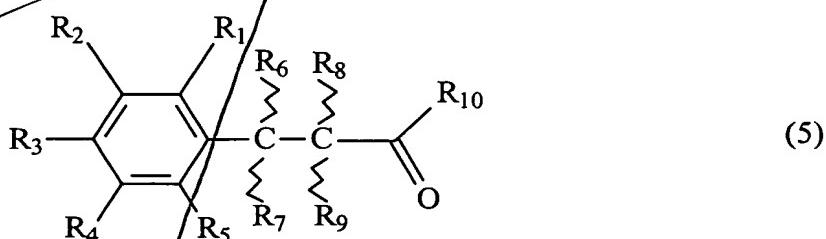
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where R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_8 have the same meaning as R_1 , R_2 , R_3 , R_4 , R_5 , R_6 and R_8 , respectively in the above formula (1);

with an aspartame compound shown by the above-mentioned general formula (3).

The compound of formula (1) can be prepared by reacting under reductive alkylating conditions, an aldehyde having formula (5)



where R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀ have the same meaning as R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, R₉ and R₁₀, respectively in the above formula (1);

it being noted that, if R₆ and, R₇, or R₈ and R₉ are not the same substituents, there is no particular limitation to the configuration of the carbon atoms to which R₆ and R₇, or R₈ and R₉ are linked, such that it may be (R), (S), (RS) or the like whichever is desired;

with the aspartame compound shown by the above general formula (3).

The aforementioned methods of preparing the compounds of formula (1) include a reacting step under the reductive alkylation conditions, and may also include other reactive steps. An additional step or steps may be included, following the reacting step under the reductive alkylation condition, for example, de-protection in a hydroxyl group or the other functional group and/or a salt forming step or the like. Such methods of protection and deprotection can be performed as described in T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis", John Wiley and Sons, Inc. (1999).

As the substituent that can be converted into a hydrogen atom under the reductive alkylation condition, those that are known in the art which can be used for such purpose, e.g., benzyloxy carbonyl group or the like, may be optionally selected depending on the particular reductive alkylation conditions employed in the reaction. As these reductive alkylation conditions, the conditions as known in the art, or any suitable conditions that will be developed in future, such as a condition employing metal hydrides, may be used, as needed.

Additional embodiments of the present invention, if aldehydes shown by the general formulas (2), (4) or (5) include hydroxyl groups, the aforementioned preparation methods may employ an aldehyde, the hydroxyl group of which is protected by a suitable protecting group, such as benzyl group.

Salts of the compounds of the present invention include, for example, salts of alkali metals such as sodium and potassium, salts of alkali earth metals, such as calcium and magnesium, ammonium salt with ammonia, salts with amino acids, such as lysine and arginine, salts with inorganic acids, such as hydrogen chloride and sulfuric acid, salts with organic acids, such as citric acid and acetic acid, and salts with sweetening agents, such as saccharin, acesulfame, cyclamic acid and glycyrrhizic acid. The preparation of the salts of the present compound of formula(1) can be prepared as known in the art.

The N-alkylaspartyl dipeptide ester compound of the present invention can be synthesized by reductive alkylation of aspartame or aspartame compounds, that is compounds obtained by replacing an L-phenylalanine methylester moiety in the aspartame by another amino acid ester, using a 3-phenylpropionaldehyde compound, a cinnamaldehyde compound or a (2-phenylethyl) alkylketone compound, which has different substituents on a phenyl group and also having one to four alkyl substituents on the main chain, and a reducing agent, such as a hydrogen/palladium carbon catalyst. Alternatively, the N-alkylaspartyl dipeptide ester compound of the present invention can be produced by reductive alkylation of an aspartame compound, having a protecting group in a β -position in the carboxylic acid, such as β -O-benzyl- α -L-aspartyl-L-amino acid methyl ester, using the above-described 3-phenylpropionaldehyde compound, a cinnamaldehyde compound or a (2-phenylethyl) alkylketone compound, and a reducing agent, such as $\text{NaB(OAc)}_3\text{H}$, as disclosed in A. F. Abdel - Magid et al., Tetrahedron letters, 31, 5595 (1990), followed by removal of protecting groups thereof, or by a method consisting in saturating unsaturated bonds with a reducing agent, as the occasion may demand. The above aspartame compound may be obtained by a usual peptide synthesis method, as discussed in Izumiya et al., Fundamentals and Experimentation in Peptide Synthesis. Published by MARUZEN on January 20, 1985. The method for synthesis of the compounds in the present invention is, however, not limited to these methods. In place of the above-mentioned 3-phenylpropionaldehyde compound, cinnamaldehyde compound or the (2-phenylethyl) alkyl ketone compound, acetal or ketal compounds thereof may, of course, be used as the aldehyde or ketone components at the time of the reductive alkylation.

As a result of sensory evaluation, the present compounds and salts thereof were found to have strong sweetening potency and have sensory (organoleptic) properties similar to that of sugar. For example, the sweetness of N-[N-[3-(3-hydroxy-4-methoxyphenyl)-3-

methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was approximately 70000 times
that of sugar, the sweetness of N-[N-[3-(3-methyl-4
hydroxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was
approximately 70000 times that of sugar, the sweetness of N-[N-[3-(3-hydroxy-4-
5 methylphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was
approximately 60000 times that of sugar, and the sweetness of N-[N-((RS)-3-(3
hydroxy-4-methoxyphenyl) butyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was
approximately 50000 times that of sugar. On the other hand, the half life in a buffer
of pH = 3.0 at 72.0 °C of N-[N-[3-(3-methoxy-4-hydroxyphenyl)-3-methylbutyl]-L- α -
10 aspartyl]-L-phenylalanine 1-methyl ester was 34.4 hours, which was substantially equivalent
to the half life of N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine 1-methyl
ester (31.4 hours under the same condition). Also, the half life in a buffer with pH=3.0 at
70.0 °C of aspartame, N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine 1-methyl
ester, N-[N-[3-(3-hydroxy-4-methoxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine
15 1- methyl ester and N-[N-(3-(4-hydroxyphenyl)-3-methylbutyl]-L- α -aspartyl)-L-
phenylalanine 1-methylester, was measured, and found to be 23.5, 38.3, 44.5 and 43.6 hours,
respectively. Sensory evaluations can be performed as described in, for example, B.T. Carr,
S.D. Pecore, K.M. Gibes and G.E. Dubois, "Sensory Methods for Sweetner Evaluation" in
Flavor Measurement, edited by C.T. Ho and C.H. Manley, Marcel Decker, Inc. (1992).

20 The present application is a Continuation Application of PCT/JP99/04977 filed
September 10, 1999 which claims priority to JP10-264252 filed September 18, 1998 and
JP11-169419 filed June 16, 1999. The contents of theses documents are herein incorporated
by reference into the present specification

Having generally described this invention, a further understanding can be obtained by
25 reference to certain specific examples which are provided herein for purposes of illustration
only, and are not intended to be limiting unless otherwise specified.

EXAMPLES

In the following examples, the NMR spectra were measured using Varian Gemini 300 (300 MHz) and MS spectra were measured using Thermo Quest TSQ700.

5 (Example 1)

Synthesis of N-[N-[3-(3-hydroxy-4-methoxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 10)

To 703 mg (1.45 mmol) of N-t-butoxycarbonyl- β -O-benzyl-(α -L-aspartyl-L-phenylalanine methyl ester, 10 ml of a 4N-HCl/dioxane solution were added and stirred at room temperature for one hour. The reaction solution was concentrated under reduced pressure. To the residue were added 50 ml of a 5%-aqueous solution of sodium hydrogen carbonate and extraction was made twice with 50 ml of ethyl acetate. An organic layer was washed with a saturated saline water and dried over anhydrous magnesium sulfate. Magnesium sulfate was filtered off and the liquid filtrate was concentrated under reduced pressure to yield 557 mg (1.45 mmol) of (3-O-benzyl-(α -L-aspartyl-L-phenylalanine methyl ester, as a viscous oily substance.

557 mg (1.45 mmol) of the above β -O-benzyl- α -L-aspartyl-L-phenylalanine methyl ester were dissolved in 15 ml of tetrahydrofuran (THF) to yield a solution which was maintained at 0 °C. To this solution were added 432 mg (1.45 mmol) of 3-(3-benzyloxy-4-methoxyphenyl)-3-methylbutyl aldehyde, 0.083 ml (1.45 mmol) of acetic acid and 462 mg (2.18 mmol) of NaB(OAc)₃H and stirred for one hour at 0 °C and overnight at room temperature. To the reaction solution were added 50 ml of a saturated aqueous solution of sodium hydrogen carbonate and extraction was made twice with 50 ml of ethyl acetate. An organic layer was washed with a saturated saline water and dried over anhydrous magnesium sulfate. Magnesium sulfate was filtered off and the liquid filtrate was concentrated under reduced pressure. The residue was purified with preparative thin layer chromatography (PTLC) to yield 832 mg (1.25 mmol) of N-[N-[3-(3-benzyloxy-4-methoxyphenyl)-3-methylbutyl]-3-O-benzyl-L- α -aspartyl]-L-phenylalanine 1-methylester as a viscous oily substance.

The above 832 mg (1.25 mmol) of N-[N-[3-(3-benzyloxy-4-methoxyphenyl)-3-methylbutyl]- β -O-benzyl-L- α -aspartyl]-L-phenylalanine 1-methyl ester were dissolved in a mixed solvent of 25 ml of methanol and 2 ml of water, and 350 mg of 10% palladium carbon

(containing 50% of water) were added thereto. The resulting mixture was reduced at room temperature for three hours under a hydrogen atmosphere. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified with PTLC to remove an odor adsorbed to yield 400 mg (0.82 mmol) of N-[N-[3-(3-hydroxy-4-methoxyphenyl)-3-methylbutyl]-L- α -L-aspartyl]-L-phenylalanine L-methylester as a solid substance.

5 ^1H MMR (DMSO-d₆) δ : 1.14 (s, 6H), 1.54-1.68 (m, 2H), 2.04-2.22 (m, 3H), 2.24-2.34 (dd, 1H), 2.84-2.94 (dd, 1H), 3.00-3.08 (dd, 1H), 3.31-3.36 (m, 1H), 3.59 (s, 3H), 3.71 (s, 3H), 4.46-4.55 (m, 1H), 6.60-6.65 (dd, 1H), 6.73 (s, 1H), 6.80 (d, 1H), 7.10-7.28 (m, 5H),
10 8.45 (d, 1H), 8.75 (brs, 1H).

ESI (Electrospray Ionization)-MS 487.3 (MH⁺)

Sweetness (sweetening potency), 70000 times the sweetness of sugar

(Example 2)

15 Synthesis of N- [N- [3- (4-methoxyphenyl) -3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 7)

N-[N-[3-(4-methoxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 72.2%, in the same way as in Example 1, except using 3-(4-methoxyphenyl)-3-methylbutyl aldehyde in place of 3-(3-benzyloxy-4-methoxyphenyl)-3-methylbutyl aldehyde.

20 ^1H MMR (DMSO-d₆) δ : 1.17 (s, 6H), 1.62-1.72 (m, 2H), 2.04-2.20 (m, 3H), 2.24-2.34 (dd, 1H), 2.84-2.94 (dd, 1H), 2.95-3.07 (dd, 1H), 3.30-3.35 (m, 1H), 3.51 (s, 3H), 3.70 (s, 3H), 4.46-4.54 (m, 1H), 6.83 (d, 2H), 7.14-7.28 (m, 7H), 8.43 (d, 1H).

ESI-MS 471.3 (MH⁺)

25 Sweetness, 25000 times the sweetness of sugar

(Example 3)

Synthesis of N-[N-[3-(4-hydroxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1 methyl ester (Table 1, compound number 8)

30 N-[N-[3-(4-hydroxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 64.5%, in the same way as in Example 1, except using 3-(4-benzyloxyphenyl)-3-methylbutyl aldehyde in place of 3-(3-

benzyloxy-4-methoxyphenyl)-3-methylbutyl aldehyde.

¹HMMR (DMSO-d₆) δ :1.15 (s, 6H), 1.58-1.72 (m, 2H), 2.04-2.20 (m, 3H), 2.24-2.34 (dd, 1H), 2.85-2.94 (dd, 1H), 3.00-3.08 (dd, 1H), 3.30-3.36 (m, 1H), 3.59 (s, 3H), 4.464.55 (m, 1H), 6.67 (d, 2H), 7.07 (d, 2H), 7.10-7.27 (m, 5H), 8.44 (d, 1H) , 9.15 (brs, 1H).

5 ESI-MS 457.3 (MH⁺)

Sweetness, 25000 times the sweetness of sugar

(Example 4)

Synthesis of N-[N-[3-(3-methoxy-4-hydroxyphenyl)-3-methylbutyl]-L-α-aspartyl]-L-

10 phenylalanine 1 methyl ester (Table 1, compound number 9)

N- [N-[3-(3-methoxy-4-hydroxyphenyl)-3-methylbutyl]-L(α-aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 62.2%, in the same way as in Example 1, except using 3-(3-methoxy-4-benzyloxyphenyl)-3-methylbutyl aldehyde in place of 3-(3-benzyloxy-4-methoxyphenyl)-3-methylbutyl aldehyde.

15 ¹HMMR (DMSO-d₆) δ :1.17 (s, 6H), 1.63-1.,72 (m, 2H), 2.08-2.22 (m, 3H), 2.25-2.33 (dd, 1H), 2.86-2.94 (dd, 1H), 3.00-3.08 (dd, 1H), 3 .33-3 .38 (m, 1H), 3.59 (s, 3H), 3 .75 (s, 3H), 3.473.55 (m, 1H), 6.67 (s, 2H), 6.81 (s, 1H), 7.14-7.27 (m, 5H), 8.46 (d, 1H), 8.70 (brs, 1H).

20 ESI-MS 487.3 (MH⁺)

Sweetness, 40000 times the sweetness of sugar

(Example 5)

Synthesis of N-[N-[3-(3-hydroxy-4-methoxyphenyl)-3-methylbutyl] -L-α-aspartyl] -L- ((α-methyl) phenylalanine 1-methylester (Table 1, compound number 22)

25 N-(N-[3'-(3-hydroxy-4-methoxyphenyl)-3-methylbutyl]-L-α-aspartyl]-L-(α-methyl) phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 77.2%, in the same way as in Example 1, except using N-t-butoxycarbonyl-β-O-benzyl-(α-L-aspartyl-L-(α-methyl) phenylalanine methyl ester in place of N-t-butoxy carbonyl-β-O-benzyl-α-L-aspartyl-L-phenylalanine methyl ester.

30 ¹HMMR (DMSO-d₆) δ :1.18 (s, 6H), 1.22 (s, 3H), 1.66-1.76 (m, 2H), 2.18-2.38 (m, 4H), 3.00 (d, 1H), 3.19 (d, 1H), 3.36-3.42 (m, 1H), 3.49 (s, 3H), 3.72 (s, 3H), 6.67 (dd, 1H), 6.74 (d, 1H), 6.80 (d, 1H), 7.02-7.06 (m, 2H), 7.20-7.30 (m, 3H), 8.29 (brs, 1H), 8.75 (brs,

1H).

ESI-MS 501.3 (MH^+)

Sweetness, 40000 times the sweetness of sugar

5 (Example 6)

Synthesis of N-[N-[3-(2-hydroxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 13)

N-[N-[3-(2-hydroxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 64.5%, in the same way as in Example 1, except using 3-(2-benzyloxyphenyl)-3-methylbutyl aldehyde in place of 3-(3-benzyloxy-4-methoxyphenyl)-3-methylbutyl aldehyde.

^1H NMR (DMSO-d₆) δ : 1.26 (s, 6H), 1.84-2.30 (m, 6H), 2.88 (dd, 1H), 3.02 (dd, 1H), 3.32-3.38 (m, 1H), 3.59 (s, 3H), 4.45-4.54 (m, 1H), 6.68-6.78 (m, 3H), 6.96-7.06 (m, 2H), 7.12-7.30 (m, 5H), 8.50 (d, 1H), 9.30 (brs, 1H) .

15 ESI-MS 457.4 (MH^+)

Sweetness, 8000 times the sweetness of sugar

(Example 7)

Synthesis of N-[N-[3-(2-hydroxy-4-methoxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 14)

N-[N-[3-(2-hydroxy-4-methoxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 44.1%, in the same way as in Example 1, except using 3-(2-benzyloxy-4-methoxyphenyl)-3-methylbutyl aldehyde in place of 3-(3-benzyloxy-4-methoxyphenyl)-3-methylbutyl aldehyde.

^1H NMR (DMSO-d₆) δ : 1.22 (s, 6H), 1.82-2.20 (m, 5H), 2.26 (dd, 1H), 2.88 (dd, 1H), 3.01 (dd, 1H), 3.34-3.40 (m, 1H), 3.59 (s, 3H), 3.64 (s, 3H), 4.46-4.53 (m, 1H), 6.28 (dd, 1H), 6.36 (d, 1H), 6.92 (d, 1H), 7.14-7.26 (m, 5H), 8.52 (d, 1H), 9.40 (brs, 1H) .

25 ESI-MS 487.3 (MH^+)

Sweetness, 20000 times the sweetness of sugar

(Example 8)

Synthesis of N-[N-[3-(2-hydroxy-4-methylphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 15)

N-[N-[3-(2-hydroxy-4-methylphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 45.1%, in the same way as in Example 1, except using 3-(2-benzyloxy-4-methylphenyl)-3-methylbutyl aldehyde in place of 3-(3-benzyloxy-4-methoxyphenyl)-3-methylbutyl aldehyde.

5 ¹HMMR (DMSO-d₆) δ : 1.23 (s, 6H), 1.82-2.20 (m, 5H), 2.14 (s, 3H), 2.25 (dd, 1H), 2.88 (dd, 1H), 3.01 (dd, 1H), 3.33-3.39 (m, 1H), 3.58 (s, 3H), 4.46-4.54 (m, 1H), 6.51 (d, 10 1H), 6.87 (s, 1H), 6.90 (d, 1H), 7.10-7.23 (m, 5H), 8.51 (d, 1H), 9.20 (brs, 1H).

ESI-MS 471.2 (MH⁺)

Sweetness, 25000 times the sweetness of sugar

(Example 9)

Synthesis of N-[N-[3-(3,4-methylenedioxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine-1-methyl ester (Table 1, compound number 16)

15 N-[N-[3-(3,4-methylenedioxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 69.7%, in the same way as in Example 1, except using 3-(3,4-methylenedioxy phenyl)-3-methylbutyl aldehyde in place of 3-(3-benzyloxy-4 -methoxyphenyl)-3-methylbutyl aldehyde.

20 ¹HMMR (DMSO-d₆) δ : 1.16 (s, 6H), 1.60-1.70 (m, 2H), 2.05-2.20 (m, 3H), 2.27 (dd, 1H), 2.89 (dd, 1H), 3.03 (dd, 1H), 3.31-3.35 (m, 1H), 3.59 (s, 3H), 4.46-4.54 (m, 1H), 5.94 (s, 2H), 6.72 (dd, 1H), 6.79 (d, 1H), 6.88 (d, 1H), 7.15-7.28 (m, 5H), 8.44 (d, 1H).

25 ESI-MS 485.4 (MH⁺)

Sweetness, 30000 times the sweetness of sugar

(Example 10)

Synthesis of N-[N-[3-(3-methyl-4-methoxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1- methyl ester (Table 1, compound number 17)

30 N-[N-[3-(3-methyl-4-methoxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 66.0%, in the same way as in Example 1, except using 3-(3-methyl-4-methoxyphenyl)-3-methylbutyl aldehyde

in place of 3-(3-benzyloxy-4-methoxy phenyl)-3-methylbutyl aldehyde.

¹HMMR (DMSO-d₆) δ : 1.16 (s, 6H), 1.63-1.72 (m, 2H), 2.13 (s, 3H), 2.08-2.20 (m, 3H), 2.25-2.32 (dd, 1H), 2.85-2.95 (dd, 1H), 3.00-3.06 (dd, 1H), 3.31-3.36 (m, 1H), 3.59 (s, 3H), 3.73 (s, 3H) , 4.47-4.55 (m, 1H), 6.79-6.82 (m, 1H), 7.037.06 (m, 2H), 7.15-7.27 (m, 5H), 8.44-8.47 (d, 1H).

ESI-MS 485.5 (MH⁺)

Sweetness, 30000 times the sweetness of sugar

(Example 11)

10 Synthesis of N-[N-[3-(3-methyl-4-hydroxyphenyl)-3-methylbutyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 18)

N-[N-[3-(3-methyl-4-hydroxyphenyl)-3-methylbutyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 63.2%, in the same way as in Example 1, except using 3-(3-methyl-4-benzyloxyphenyl)-3-methylbutyl aldehyde in place of 3-(3-benzyloxy-4-methoxyphenyl)-3-methylbutyl aldehyde.

¹HMMR (DMSO-d₆) δ : 1.14 (s, 6H), 1.59-1.68 (m, 2H), 2.09 (s, 3H), 2.09-2.18 (m, 3H), 2.25 (dd, 1H), 2.90 (dd, 1H), 3.02 (dd, 1H), 3.30-3.36 (m, 1H), 3.59 (s, 3H), 4.46-4.54 (m, 1H), 6.68 (d, 1H), 6.88 (dd, 1H), 6.96 (s, 1H), 6.14-6.73 (m, 5H), 8.46 (d, 1H), 9.01 (brs, 1H).

ESI-MS 471.4 (MH⁺)

Sweetness, 70000 times the sweetness of sugar

(Example 12)

20 Synthesis of N-[N-[2-[1-(3-methoxy-4-hydroxyphenyl) cyclopentyl] ethyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 20)

N-[N-(2-[1-(3-methoxy-4-hydroxyphenyl) cyclopentyl]ethyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance, with a total yield of 68.4%, in the same way as in Example 1, except using 2-[1-(3-methoxy-4-hydroxyphenyl) cyclopentyl] acetaldehyde in place of 3(3-benzyloxy-4-methoxyphenyl)-3-methylbutyl aldehyde.

¹HMMR (DMSO-d₆) δ : 1.48-1.82 (m, 10H) , 2.00-2.16 (m, 3H), 2.24 (dd, 1H), 2.90 (dd, 1H), 3.01 (dd, 1H), 3.30-3.40 (m, 1H), 3.59 (s, 3H), 3.74 (s, 3H), 4.45-4. 53 (m, 1H),

6.59 (dd, 1H), 6.65 (d, 1H), 6.75 (dd, 1H), 7.14-7.28 (m, 5H), 8.44 (d, 1H), 8.70 (brs, 1H).

ESI-MS 513.4 (MH^+)

Sweetness, 30000 times the sweetness of sugar

5 (Example 13)

Synthesis of N-[N-[3-(3-hydroxy-4-methoxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1- ethyl ester (Table 1, compound number 21)

N-[N-[3-(3-hydroxy-4-methoxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1- ethyl ester was obtained as a solid substance, with a total yield of 56.1%, in
10 the same way as in Example 1, except using N-t-butoxycarbonyl- β -O-benzyl- α -L-aspartyl-L-phenylalanine ethyl ester in place of N-t-butoxycarbonyl- β -O-benzyl- α -L-aspartyl-L-phenylalanine methyl ester.

15 ¹H NMR (DMSO-d₆) δ : 1.09-1.13 (m, 9H), 1.58-1.67 (m, 2H), 2.08-2.37 (m, 4H),
2.86-2.93 (dd, 1H), 2.99-3.06 (dd, 1H), 3.32-3.37 (m, 1H), 3.71 (s, 3H), 4.00-4.07 (m, 2H),
4.44-4.51 (m, 1H), 6.62-6.65 (d, 1H), 6.74-6.81 (m, 2H), 7.15-7.27 (m, 5H), 8.46 (d, 1H),
8.78 (brs, 1H)

20 ESI-MS 501.3 (MH^+)

Sweetness, 15000 times the sweetness of sugar

20 (Example 14)

Synthesis of N-[N-[(RS)-3-(3-methoxy-4-hydroxyphenyl) butyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 3)

25 419 mg (1.09 mmol) of β -O-benzyl- α -L-aspartyl-L-phenylalanine methyl ester, obtained in the same way as in Example 1, were dissolved in 10 ml of THF and the resulting solution was maintained at 0°C. To this solution were added 308 mg (1.09 mmol) of 3- β -methoxy-4-benzyloxyphenyl)-2-butenal, 0.062 ml (1.09 mmol) of acetic acid and 345 mg (1.63 mmol) of NaB (OAc)₃H and the resulting mixture was stirred at 0°C for one hour and further stirred overnight at room temperature. To the reaction solution were added 30 ml of a saturated aqueous solution of sodium hydrogen carbonate and extraction was carried out
30 twice with 30 ml of ethyl acetate. An organic layer was washed with saturated saline water and dried over anhydrous magnesium sulfate. After filtering magnesium sulfate off, the liquid filtrate was concentrated under reduced pressure. The residue was purified with

preparative thin layer chromatography (PTLC) to obtain 534 mg (0.82 mmol) of N-[N-[3-(3-methoxy-4-benzyloxyphenyl)2-but enyl]-β-O-benzyl-L-α-aspartyl]-L-phenylalanine 1-methyl ester as a viscous oily substance.

5 534 mg (0.82 mmol) of the above N-[N-[3-(3-methoxy-4-benzyloxyphenyl)-2-but enyl]-β-O-benzyl-L-α-aspartyl]-L-phenylalanine 1-methyl ester were dissolved in a mixed solvent of 20 ml of methanol and 1 ml of water. To the resulting mixture were added 200 mg of 10% palladium carbon (containing 50% of water). The resulting mixture was reduced at room temperature for three hours in a hydrogen atmosphere. The catalyst was filtered off and the resulting filtrate was concentrated under reduced pressure. The residue
10 10 was purified with PTLC to remove an odor adsorbed to obtain 269 mg (0.57 mmol) of N- [N- [(RS) -3- (3-methoxy-4-hydroxyphenyl) butyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester as a solid substance.

15 15 ¹HMMR (DMSO-d₆) δ :1.10 (2d, 3H), 1.50-1.60 (m, 2H), 2.102.40 (m, 4H), 2.55-2.65 (m, 1H), 2.81-2.95 (m, 1H), 3.033.09 (dd, 1H), 3.34-3.40 (m, 1H), 3.60 (s, 1.5H), 3.61 (s, 1.5H), 3.74 (s, 1.5H), 3.75 (s, 1.5H), 4.50-4.60 (m, 1H), 6.55 (d, 1H), 6.67 (d, 1H), 6.72 (s, 1H), 7.15-7.30 (m, 5H), 8.50 (brd, 1H), 8.70 (brs, 1H).

20 20 ESI-MS 473.3 (MH⁺)

Sweetness, 30000 times the sweetness of sugar

25 25 (Example 15)

Synthesis of N-[N-[(RS)-3-(4-methoxyphenyl) butyl]-L-α-aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 1)

N-[N-[(RS)-3-(4-methoxyphenyl) butyl]-L-aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance with a total yield of 37.3 %in the same way as in Example
25 25 14 except using 3-(4-methoxyphenyl)-2-but enal in place of 3-(3-methoxy-4-benzyloxyphenyl)-2-but enal.

30 30 ¹HMMR (DMSO-d₆) δ :1.09 (d, 1.5H), 1.11 (d, 1.5H), 1.54 (m, 2H), 2 .17-2.23 (m, 3H), 2.28-2.38 (m, 1H), 2.64 (m, 1H), 2.85-2.95 (m, 1H), 3.02-3.10 (dd, 1H), 3.60 (s, 1.5H), 3.61 (s, 1.5H), 3.70 (s, 1H) , 4.54 (m, 1H), 6. 83 (d, 2H), 7.07 (d, 2H) , 7.18-7.28 (m, 5H).

ESI-MS 457.3 (MH⁺)

Sweetness, 16000 times the sweetness of sugar

(Example 16)

Synthesis of N-[N-[(RS)-3-(3-hydroxyphenyl) butyl]-L- α -aspartyl]-L-phenylalanine 1 methyl ester (Table 1, compound number 2)

N-[N-[(RS)-3-(3-hydroxyphenyl) butyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance with a total yield of 31.1% in the same way as in Example 14 except using 3-(3-benzyloxyphenyl)-2-butenal in place of 3-(3-methoxy-4-benzyloxyphenyl)-2-butenal.

¹HMMR (DMSO-d₆) δ : 1.09 (m, 3H), 1.55 (m, 2H), 2.10-2.24 (m, 3H), 2.26-2.34 (dd, 1H), 2.58 (m, 1H), 2.85-2.98 (m, 1H), 3.01-3.10 (dd, 1H), 3.60 (s, 1.5H), 3.61 (s, 1.5H), 4.53 (m, 1H), 6.55-6.62 (m, 3H), 7.05 (t, 1H), 7.16-7.30 (m, 5H), 8.47 (m, 1H), 8.75 (brs, 1H).

ESI-MS 443.2 (MH⁺)

Sweetness, 12000 times the sweetness of sugar

(Example 17)

Synthesis of N-[N-[(RS)-3-(3-hydroxy-4-methoxyphenyl) butyl]-L- α -aspartyl]-L-phenylalanine 1- methyl ester (Table 1, compound number 4)

N-[N-[(RS) -3- (3-hydroxy-4-methoxyphenyl) butyl] -L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance with a total yield of 38.8% in the same way as in Example 14 except using 3-(3-benzyloxy-4-methoxyphenyl)-2-butenal in place of 3-(3-methoxy-4-benzyloxyphenyl)-2-butenal.

¹HMMR (DMSO-d₆) δ : 1.08 (m, 3H), 1.53 (m, 2H), 2.13-2 .21 (m, 3H), 2.28 (dd, 1H), 2.56 (m, 1H), 2.86-3.00 (m, 1H), 3.023.12 (dd, 1H), 3.29-3.40 (m, 1H), 3.60 (s, 1.5H), 3.61 (s, 1.5H), 3.71 (s, 3H) , 4.53 (m, 1H), 6.53 (d, 1H), 6.60 (d, 1H), 6.79 (d, 1H), 7.15-7.26 (m, 5H), 8.46 (m, 1H), 8.75 (brs, 1H).

ESI-MS 473.3 (MH^{*})

Sweetness, 50000 times the sweetness of sugar

(Example 18)

Synthesis of N-[N-[3-(RS)-3-hydroxy-4-methoxyphenyl) butyl] -L- α -aspartyl]-3-cyclohexyl-L-alanine 1-methyl ester (Table 1, compound number 6)

N-[N-[(RS)-3-(3-hydroxy-4-methoxyphenyl) butyl]-L- α -aspartyl]-3-cyclohexyl-L-alanine 1-methyl ester was obtained as a solid substance with a total yield of 41.7% in the

same way as in Example 14 except using N-t-butoxycarbonyl- β -O-benzyl- α -L-aspartyl-3-cyclohexyl-Lalanine methyl ester in place of N-t-butoxycarbonyl- β -O-benzyl- α -L-aspartyl-L-phenylalanine methyl ester and also except using 3-(3-benzyloxy-4-methoxyphenyl)-2-butenal in place of 3-(3-methoxy-4-benzyloxyphenyl)-2-butenal.

5 ^1H MMR (DMSO-d₆) δ : 0.75-1.34 (m, 5H), 1.11 (d, 3H), 1.501.70 (m, 1H), 2.18-2.28 (m, 2H), 2.35-2.45 (m, 2H), 2.58-2.65 (m, 1H), 3.27-3.36 (m, 1H), 3.60 (m, 3H), 3.71 (s, 3H), 4.35 (m, 1H), 6.53-6.60 (m, 1H), 6.61 (d, 1H), 6.79 (d, 1H), 8.44 (m, 1H), 8.80 (brs, 1H).

10 ESI-MS 479.4 (MH⁺)

10 Sweetness, 40000 times the sweetness of sugar

0 (Example 19)

Synthesis of N-[N-[(RS)-3-(3-methoxy-4-hydroxyphenyl) butyl]-L- α -aspartyl]-L-tyrosine 1-methyl ester (Table 1, compound number 5)

15 N-[N-[(RS)-3-(3-methoxy-4-hydroxyphenyl)-butyl]-L- α -aspartyl]-L-tyrosine 1-methyl ester was obtained as a solid substance with a total yield of 37.5% in the same way as in Example 14 except using N-t-butoxycarbonyl- β -O-benzyl- α -L aspartyl-L-tyrosine methyl ester in place of N-t-butoxycarbonyl- β -O-benzyl- α -L-aspartyl-L-phenylalanine methyl ester.

20 ^1H MMR (DMSO-d₆) δ : 1.10 (d, 3H), 1.55 (m, 2H), 2.16-2.41 (m, 4H), 2.58 (m, 1H), 2.70-2.82 (m, 1H), 2.85-2.95 (dd, 1H), 3.58 (s, 3H), 3.78 (s, 3H), 4.43 (m, 1H), 6.53 -6.75 (m, 5H), 6.96 (d, 2H), 8.49 (brd, 1H), 8.75 (brs, 1H), 9.80 (brs, 1H)

25 ESI-MS 489.3 (MH⁺)

25 Sweetness, 25000 times the sweetness of sugar

25 (Example 20)

Synthesis of N-[N-[(RS)-3-(3-methyl-4-hydroxyphenyl) butyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 11)

30 N-[N-[(RS)-3-(3-methyl-4-hydroxy phenyl) butyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance with a total yield of 19.7% in the same way as in Example 14 except using 3-(3-methyl-4-benzyloxyphenyl)-2-butenal in place of 3-(3-methoxy-4-benzyloxyphenyl)-2-butenal.

35 ^1H MMR (DMSO-d₆) δ : 1.06-1.09 (m, 3H), 1.49-1.54 (m, 2H), 2.08 (m, 3H), 2.11-

2.20 (m, 3H), 2.17-2.33 (m, 1H), 2.85- 2.95 (m, 2H), 3.05-3.09 (m, 1H), 3.33-3.37 (m, 1H),
3.61 (s, 3H), 4.50-4.55 (m, 1H), 6.65 (m, 1H), 6.76 (m, 1H), 6.84 (s, 1H), 7.16-7.28 (m, 5H),
8.47-8.50 (m, 1H), 9.02 (brs, 1H)

ESI-MS 457.2 (MH⁺).

5

Sweetness, 50000 times the sweetness of sugar

(Example 21)

Synthesis of N-[N-[3-(3-hydroxy-4-methoxyphenyl)-(RS)-2-methylpropyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 12)

10 N-[N-[3-(3-hydroxy-4-methoxyphenyl)-(RS)-2-methylpropyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance with a total yield of 45.6% in the same way as in Example 14 except using 3-(3-benzyloxy-4-methoxyphenyl)-2-methyl-2-propenal in place of 3-(3-methoxy-4-benzyloxyphenyl)-2-butenal.

15 ¹HMMR (DMSO-d₆) δ : 0.68-0.85 (m, 3H), 1.65-1.82 (m, 1H), 2.08- 2.37 (m, 2H),
2.27-2.30 (d, 4H), 2.94-3.10 (m, 2H), 3.43-3.45 (m, 1H), 3.62 (s, 3H), 3.72 (s, 3H), 4.48-4.59
(m, 1H), 6.49-6.59 (m, 2H), 6.77-6.80 (m, 1H), 7.20-7.29 (m, 5H), 8.57-8.58 (m, 1H), 8.92
(brs, 1H).

ESI-MS 473.4 (MH⁺)

Sweetness, 5000 times the sweetness of sugar

20 (Example 22)

Synthesis of N-[N-[3-(3-hydroxy-4-methylphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 19)

25 274 mg (0.97 mmol) of 3-[(3-benzyloxy-4-methyl) phenyl]-3-methylbutyl aldehyde,
353 mg (1.2 mmol) of aspartame and 100 mg of 10% palladium carbon (containing 50% of water) were added to 7 ml of methanol and stirred at room temperature for four hours in a hydrogen atmosphere. The catalyst was filtered off and the resulting filtrate was concentrated under reduced pressure. The residue was purified by preparative thin layer chromatography (PTLC) to produce 299 mg (0.64 mmol, 65.5) of N-[N-[3-(3-hydroxy-4-methylphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester as a solid substance.

30 ¹HMMR (DMSO-d₆) δ : 1.14 (s, 6H), 1.58-1, 70 (m, 2H), 2.05 (s, 3H), 2.07-2.42 (m,

4H), 2.89 (dd, 1H), 3.03 (dd, 1H), 3.30-3.40 (m, 1H), 3.59 (s, 3H), 4.46-4.54 (m, 1H), 6.60 (d, 1H), 6.73 (s, 1H), 6.94 (d, 1H), 7.15-7.30 (m, 5H), 8.46 (brs, 1H) 9.08 (brs, 1H).

ESI-MS 471.3 (MH^+)

Sweetness, 60000 times the sweetness of sugar

5

(Example 23)

Synthesis of N-[N-[3-(3,4-dihydroxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester (Table 1, compound number 23)

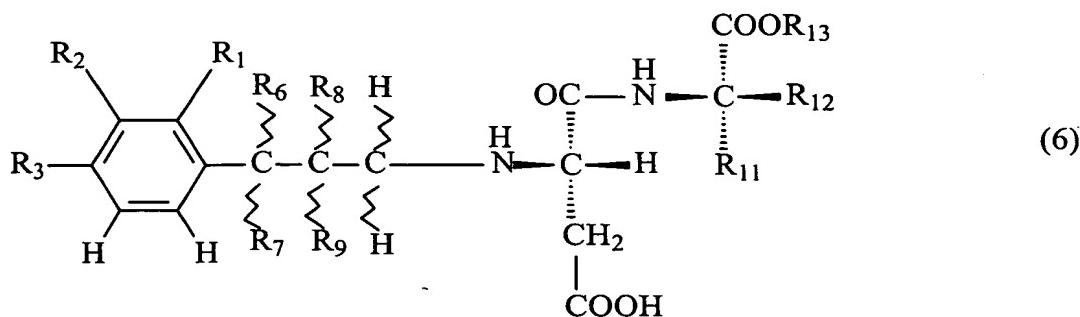
N- [N- [3-(3,4-dihydroxyphenyl)-3-methylbutyl]-L- α -aspartyl]-L-phenylalanine 1-methyl ester was obtained as a solid substance with a total yield of 76.5% in the same way as in Example 1 except using 3-(3,4-dibenzylloxyphenyl)-3methylbutyl aldehyde in place of 3-(3-benzylloxy-4-methoxyphenyl)-3-methlbuthyl aldehyde.

¹H NMR (DMSO-d₆) δ : 1.14 (s, 6H), 1.76-1.93 (m, 2H), 2.40-2.50 (m, 2H), 2.73-2.80 (m, 2H), 2.91 (dd, 1H), 3.06 (dd, 1H), 3.59 (s, 3H), 3.95-4.05 (m, 1H) 4.45-4.55 (m, 1H), 6.52 (d, 1H), 6.64-6.70 (m, 2H), 6.94 (d, 1H), 7.15-7.30 (m, 5H), 8.73 (brs, 1H), 8.80 (brs, 1H), 9.09 (brs, 1H).

ESI-MS 473.3 (MW)

Sweetness, 50000 times the sweetness of sugar

Table 1 shows the structures of several synthesized N-alkyl aspartyl dipeptide ester compounds, shown by the general formula (6) and summarizes the results of the sensory evaluation tests.



As is shown by the results in Table 1, the novel compounds of the present invention
are particularly excellent in sweetness (sweetening potency).

Structure of N-alkylasparatyl dipeptide ester compound and sweetness potency

Table 1

5	Compound										sweetness potency* ¹	
	No.	R ₁	R ₂	R ₃	R ₆	R ₇	R ₈	R ₁₁	R ₁₂	R ₁₃		
	1	H	H	OCH ₃	CH ₃	H	H	CH ₂ C ₆ H ₅	H	CH ₃	16000	
	2	H	OH	H	CH ₃	H	H	CH ₂ C ₆ H ₅	H	CH ₃	12000	
10	3	H	OCH ₃	OH	CH ₃	H	H	CH ₂ C ₆ H ₅	H	CH ₃	30000	
	4	H	OH	OCH ₃	CH ₃	H	H	CH ₂ C ₆ H ₅	H	CH ₃	50000	
	5	H	OCH ₃	OH	CH ₃	H	H	CH ₂ C ₆ H ₄ -p-OH		H	CH ₃	25000
	6	H	OH	OCH ₃ CH ₃		H	H	CH ₂ C ₆ H ₁₁	H	CH ₃	40000	
15	7	H	H	OCH ₃	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	25000	
	8	H	H	OH	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	25000	
	9	H	OCH ₃	OH	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	40000	
	10	H	OH	OCH ₃	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	70000	
	11	H	CH ₃	OH	CH ₃	H	H	CH ₂ C ₆ H ₅	H	CH ₃	50000	
20	12	H	OH	OCH ₃	H	H	CH ₃	CH ₂ C ₆ H ₅	H	CH ₃	5000	
	13	OH	H	H	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	8000	
	14	OH	H	OCH ₃	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	20000	
	15	OH	H	CH ₃	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	25000	
	16	H	OCH ₂ O		CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	30000	
25	17	H	CH ₃	OCH ₃	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	30000	
	18	H	CH ₃	OH	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	70000	
	19	H	OH	CH ₃	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	60000	
	20	H	OCH ₃	OH	CH ₂ CH ₂ CH ₂ CH ₂	CH ₂	H	CH ₂ C ₆ H ₅	H	CH ₃	30000	
	21	H	OH	OCH ₃	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₂ CH ₃	15000	
30	22	H	OH	OCH ₃	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	CH ₃	CH ₃	40000	
	23	H	OH	OH	CH ₃	CH ₃	H	CH ₂ C ₆ H ₅	H	CH ₃	50000	

*1values compared to sweetening potency of a 4 % aqueous solution of sucrose

Effect of Invention

The novel N-alkylaspartyl dipeptide ester compound according to the present invention is low in calories and exhibits a sweetening potency which is particularly superior in comparison with conventional sweetening agents. In the present invention, a novel chemical substance which has superior properties as a sweetening agent can be provided. The novel compound can be used not only for a sweetening agent but also for the affording of sweetness to foods or the like products, such as beverages (drinks) and foods, requiring sweet taste.

Obviously, numerous modifications and variations on the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.